The status of each claim in the application is provided below:

Claims 1-124: Canceled.

125. (New) A method of effecting in a subject at least one member selected from the group consisting of promoting hydration of mucosal surfaces, promoting ocular hydration, promoting corneal hydration, promoting mucus clearance in mucosal surfaces, restoring mucosal defense, preventing ventilator-induced pneumonia, treating chronic bronchitis, treating cystic fibrosis, treating sinusitis, treating vaginal dryness, treating dry eye, treating Sjogren's disease, treating distal intestinal obstruction syndrome, treating dry skin, treating esophagitis, treating dry mouth (xerostomia), treating nasal dehydration, treating chronic obstructive pulmonary disease, treating emphysema, treating pneumonia, treating constipation, treating chronic diverticulitis, treating rhinosinusitis, treating asthma, treating primary ciliary dyskinesia, and treating otitis media,

administering to a subject an effective amount of a compound represented by formula (I):


(I)
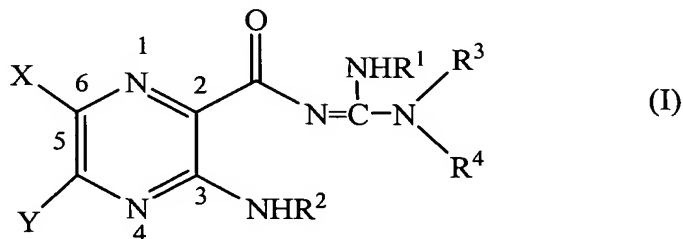
wherein

X is hydrogen, halogen, trifluoromethyl, lower alkyl, unsubstituted or substituted phenyl, lower alkyl-thio, phenyl-lower alkyl-thio, lower alkyl-sulfonyl, or phenyl-lower alkyl-sulfonyl;

Y is hydrogen, hydroxyl, mercapto, lower alkoxy, lower alkyl-thio, halogen, lower alkyl, unsubstituted or substituted mononuclear aryl, or $-N(R^2)_2$;

R^1 is hydrogen or lower alkyl;

each R^2 is, independently, $-R^7$, $-(CH_2)_m-OR^8$, $-(CH_2)_m-NR^7R^{10}$, $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$, $-(CH_2)_n-Z_g-R^7$, $-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2)_n-CO_2R^7$, or

$$\text{---}(CH_2)_n\text{---}\underset{O}{\overset{O}{\diagdown}}\diagup\overset{R^7}{\underset{R^7}{\diagup}}\quad ;$$
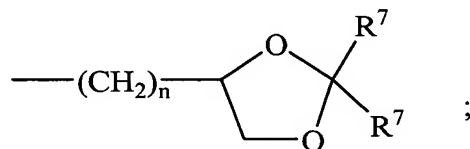
R^3 and R^4 are each, independently, hydrogen, a group represented by formula (A), lower alkyl, hydroxy lower alkyl, phenyl, phenyl-lower alkyl, (halophenyl)-lower alkyl, lower-(alkylphenylalkyl), lower (alkoxyphenyl)-lower alkyl, naphthyl-lower alkyl, or pyridyl- lower alkyl, with the proviso that at least one of R^3 and R^4 is a group represented by formula (A):

$$\text{---}(C(R^L)_2)_o\text{---}x\text{---}(C(R^L)_2)_p\diagup\overset{Q=Q\diagup R^5}{\underset{Q-Q\diagdown (R^6)_4}{\diagdown Q}} \qquad (A)$$

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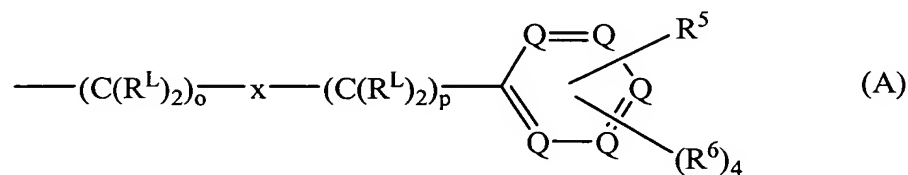
wherein

each R^L is, independently, $-R^7$, $-(CH_2)_n-OR^8$, $-O-(CH_2)_m-OR^8$,

$-(CH_2)_n-NR^7R^{10}$, $-O-(CH_2)_m-NR^7R^{10}$, $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2CH_2O)_m-R^8$,

$-O-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$,

$-O-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$,

$-O-(CH_2)_m-C(=O)NR^7R^{10}$, $-(CH_2)_n-(Z)_g-R^7$, $-O-(CH_2)_m-(Z)_g-R^7$,

$-(CH_2)_n-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-O-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-(CH_2)_n-CO_2R^7$, $-O-(CH_2)_m-CO_2R^7$, $-OSO_3H$, -O-glucuronide, -O-glucose,

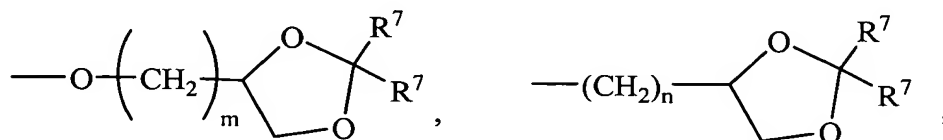, or
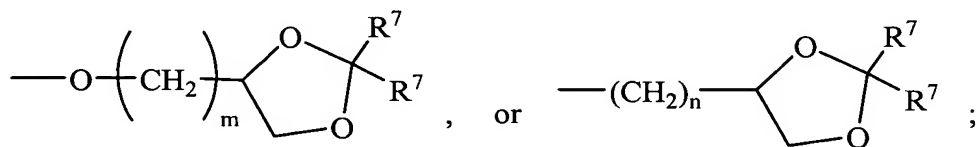
each o is, independently, an integer from 0 to 10;

each p is an integer from 0 to 10;

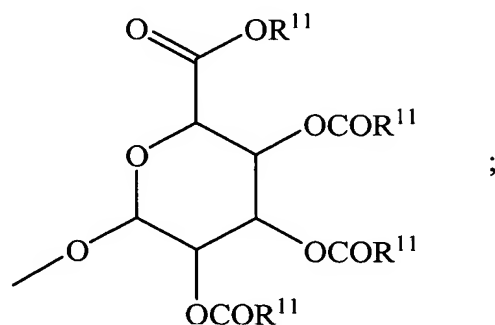with the proviso that the sum of o and p in each contiguous chain is
from 1 to 10;

each x is, independently, O, NR^{10}, C(=O), CHOH, C(=N-R^{10}),

CHNR^7R^{10}, or represents a single bond;

each R^5 is, independently, $-(CH_2)_m-OR^8$, $-O-(CH_2)_m-OR^8$,

$-(CH_2)_n-NR^7R^{10}$, $-O-(CH_2)_m-NR^7R^{10}$, $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-(CH_2CH_2O)_m-R^8$,

$-O-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$,

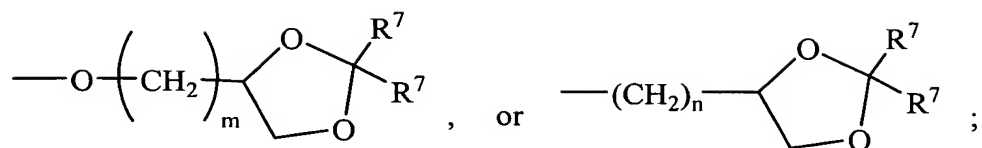$-O-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$,

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$-O-(CH_2)_m-C(=O)NR^7R^{10}$, $-(CH_2)_n-(Z)_g-R^7$, $-O-(CH_2)_m-(Z)_g-R^7$,

$-(CH_2)_n-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-O-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-(CH_2)_n-CO_2R^7$, $-O-(CH_2)_m-CO_2R^7$, $-OSO_3H$, -O-glucuronide, -O-glucose,

or

;

each R^6 is, independently, $-R^7$, $-OR^{11}$, $-N(R^7)_2$, $-(CH_2)_m-OR^8$,

$-O-(CH_2)_m-OR^8$, $-(CH_2)_n-NR^7R^{10}$, $-O-(CH_2)_m-NR^7R^{10}$,

$-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$, $-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-(CH_2CH_2O)_m-R^8$, $-O-(CH_2CH_2O)_m-R^8$, $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$,

$-O-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$, $-(CH_2)_n-C(=O)NR^7R^{10}$,

$-O-(CH_2)_m-C(=O)NR^7R^{10}$, $-(CH_2)n-(Z)_g-R^7$, $-O-(CH_2)_m-(Z)_g-R^7$,

$-(CH_2)_n-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-O-(CH_2)_m-NR^{10}-CH_2(CHOR^8)(CHOR^8)_n-CH_2OR^8$,

$-(CH_2)_n-CO_2R^7$, $-O-(CH_2)_m-CO_2R^7$, $-OSO_3H$, -O-glucuronide, -O-glucose,

$$\text{—O—}(CH_2)_m\text{—}\underset{\underset{O}{\diagdown\diagup}}{\overset{\overset{O}{\diagup\diagdown}}{}}\underset{R^7}{\overset{R^7}{\diagup}} \quad , \quad \text{or} \quad \text{—}(CH_2)_n\text{—}\underset{\underset{O}{\diagdown\diagup}}{\overset{\overset{O}{\diagup\diagdown}}{}}\underset{R^7}{\overset{R^7}{\diagup}} \quad ;$$

wherein when two R^6 are -OR^{11} and are located adjacent to each other on a phenyl ring, the alkyl moieties of the two R^6 may be bonded together to form a methylenedioxy group;

each R^7 is, independently, hydrogen or lower alkyl;

each R^8 is, independently, hydrogen, lower alkyl, -C(=O)-R^{11}, glucuronide, 2-tetrahydropyranyl, or

$$\text{structure: pyranose ring bearing } O\!\!=\!\!C\!\!-\!OR^{11}, \ OCOR^{11} \ (\times 3), \text{ and } OCH_3 \text{ substituents}$$

;
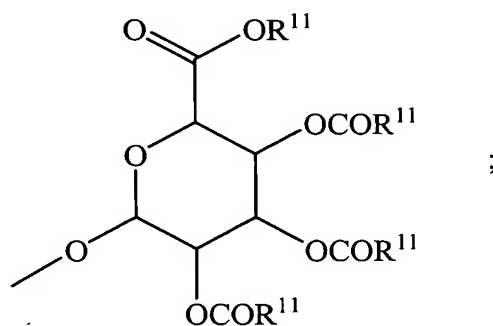
each R^9 is, independently, -CO_2R^7, -$CON(R^7)_2$, - SO_2CH_3, or -C(=O)R^7;

each R^{10} is, independently, -H, -SO_2CH_3, -CO_2R^7, -C(=O)NR^7R^9, -C(=O)R^7, or -CH_2-$(CHOH)_n$-CH_2OH;

each Z is, independently, CHOH, C(=O), $CHNR^7R^{10}$, C=NR^{10}, or NR^{10};

each R^{11} is, independently, lower alkyl;

each g is, independently, an integer from 1 to 6;

each m is, independently, an integer from 1 to 7;

each n is, independently, an integer from 0 to 7;

each Q is, independently, $C\text{-}R^5$, $C\text{-}R^6$, or a nitrogen atom, wherein at most 3 Q in a ring is a nitrogen atom;

or a pharmaceutically acceptable salt thereof, and

inclusive of all enantiomers, diastereomers, and racemic mixtures thereof.

126. (New) The method of Claim 125, wherein the subject is human.

127. (New) The method of Claim 125, wherein promoting hydration of mucosal surfaces is effected.

128. (New) The method of Claim 125, wherein promoting ocular hydration is effected.

129. (New) The method of Claim 125, wherein promoting corneal hydration is effected.

130. (New) The method of Claim 125, wherein promoting mucus clearance in mucosal surfaces is effected.

131. (New) The method of Claim 125, wherein restoring mucosal defense is effected.

132. (New) The method of Claim 125, wherein preventing ventilator-induced pneumonia is effected.

133. (New) The method of Claim 125, wherein treating chronic bronchitis is effected.

134. (New) The method of Claim 125, wherein treating cystic fibrosis is effected.

135. (New) The method of Claim 125, wherein treating sinusitis is effected.

136. (New) The method of Claim 125, wherein treating vaginal dryness is effected.

137. (New) The method of Claim 125, wherein treating dry eye is effected.

138. (New) The method of Claim 125, wherein treating Sjogren's disease is effected.

139. (New) The method of Claim 125, wherein treating distal intestinal obstruction syndrome is effected.

140. (New) The method of Claim 125, wherein treating dry skin is effected.

141. (New) The method of Claim 125, wherein treating esophagitis is effected.

142. (New) The method of Claim 125, wherein treating dry mouth (xerostomia) is effected.

143. (New) The method of Claim 125, wherein treating nasal dehydration is effected.

144. (New) The method of Claim 125, wherein treating chronic obstructive pulmonary disease is effected.

145. (New) The method of Claim 125, wherein treating emphysema is effected.

146. (New) The method of Claim 125, wherein treating pneumonia, treating constipation is effected.

147. (New) The method of Claim 125, wherein treating chronic diverticulitis is effected.

148. (New) The method of Claim 125, wherein treating rhinosinusitis is effected.

149. (New) The method of Claim 125, wherein treating asthma is effected.

150. (New) The method of Claim 125, wherein treating primary ciliary dyskinesia is effected.

151. (New) The method of Claim 125, wherein treating otitis media is effected.

152. (New) The method of Claim 125, wherein Y is $-NH_2$.

153. (New) The method of Claim 152, wherein R^2 is hydrogen.

154. (New) The method of Claim 153, wherein R^1 is hydrogen.

155. (New) The method of Claim 154, wherein X is chlorine.

156. (New) The method of Claim 155, wherein R^3 is hydrogen.

157. (New) The method of Claim 156, wherein each R^L is hydrogen.

158. (New) The method of Claim 157, wherein o is 4.

159. (New) The method of Claim 158, wherein p is 0.

160. (New) The method of Claim 159, wherein x represents a single bond.

161. (New) The method of Claim 160, wherein each R^6 is hydrogen.

162. (New) The method of Claim 161, wherein at most one Q in a ring is a nitrogen atom.

163. (New) The method of Claim 162, wherein no Q is a nitrogen atom.

164. (New) The method of Claim 161, wherein R^5 is $-(CH_2)_m-OR^8$.

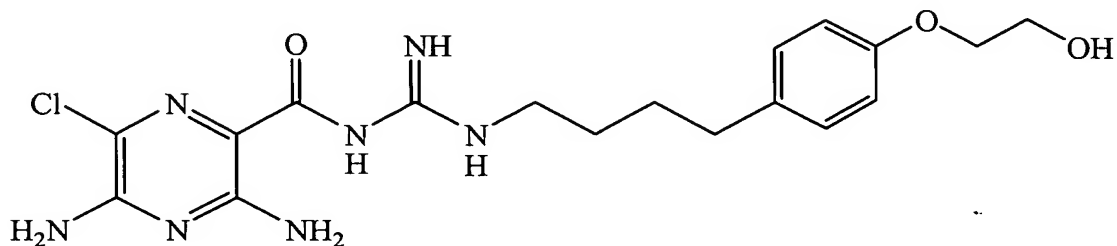165. (New) The method of Claim 164, wherein the compound is represented by the formula:
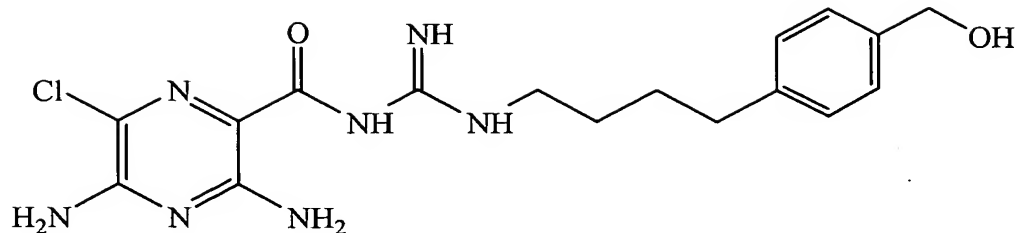
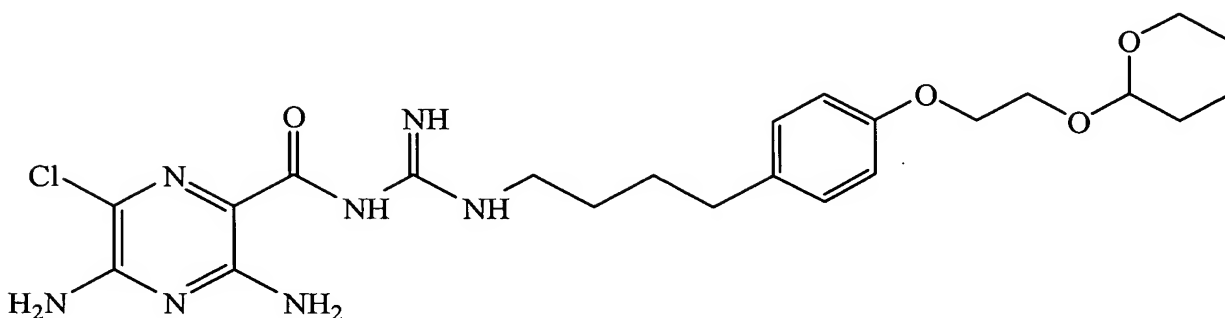166. (New) The method of Claim 164, wherein the compound is represented by the formula:
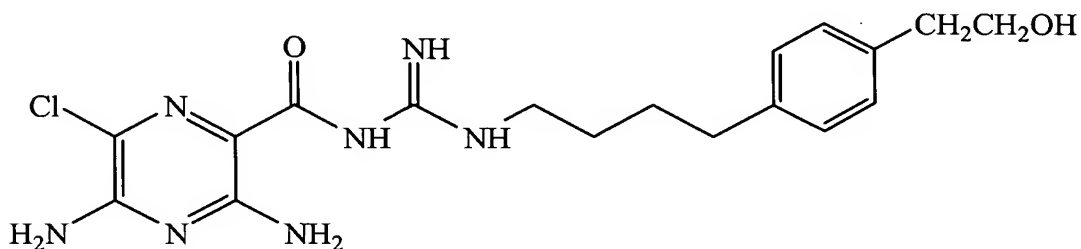
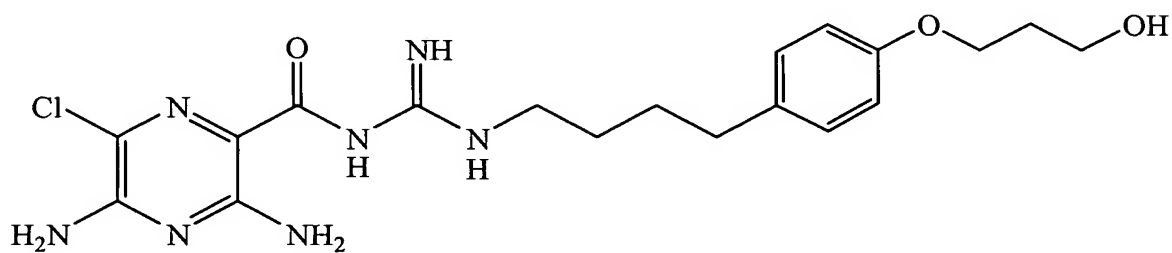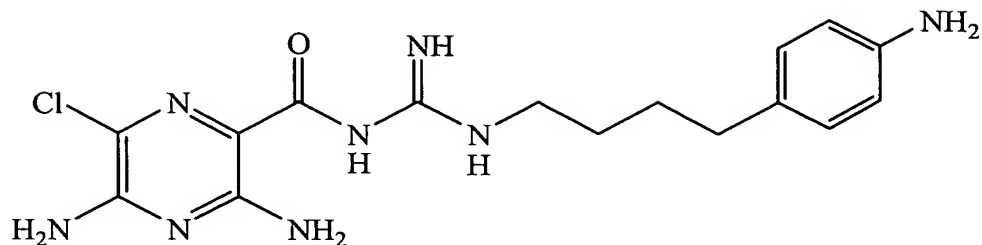167. (New) The method of Claim 161, wherein R^5 is $-O-(CH_2)_m-OR^8$.

168. (New) The method of Claim 167, wherein the compound is represented by the formula:

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169. (New) The method of Claim 167, wherein the compound is represented by the formula:

170. (New) The method of Claim 167, wherein the compound is represented by the formula:
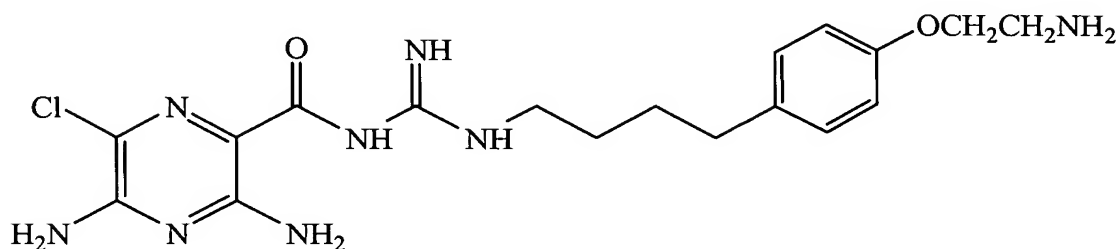

171. (New) The method of Claim 161, wherein R^5 is $-(CH_2)_n-NR^7R^{10}$.

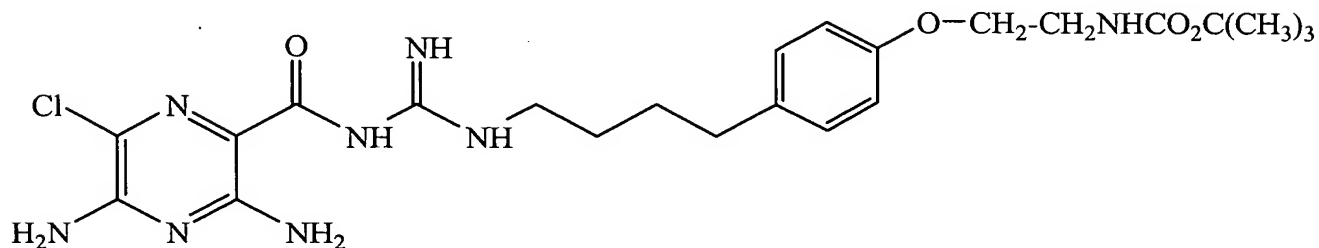172. (New) The method of Claim 171, wherein the compound is represented by the formula:

173. (New) The method of Claim 161, wherein R^5 is $-O-(CH_2)_m-NR^7R^{10}$.

174. (New) The method of Claim 173, wherein the compound is represented by the formula:
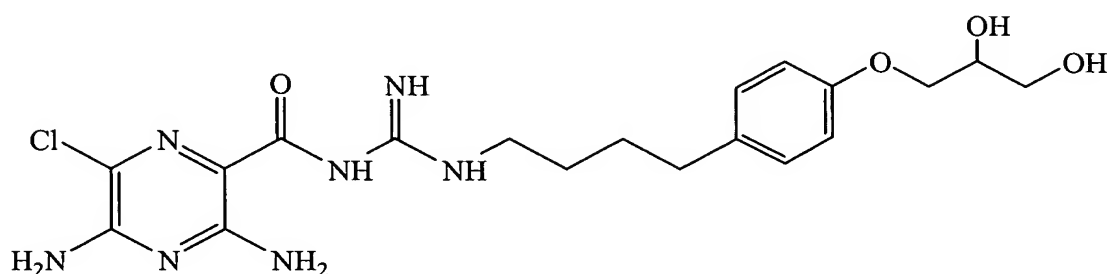

175. (New) The method of Claim 173, wherein the compound is represented by the formula:

176. (New) The method of Claim 161, wherein R^5 is $-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$.

177. (New) The method of Claim 161, wherein R^5 is

$-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$.

178. (New) The method of Claim 177, wherein the compound is represented by the formula:

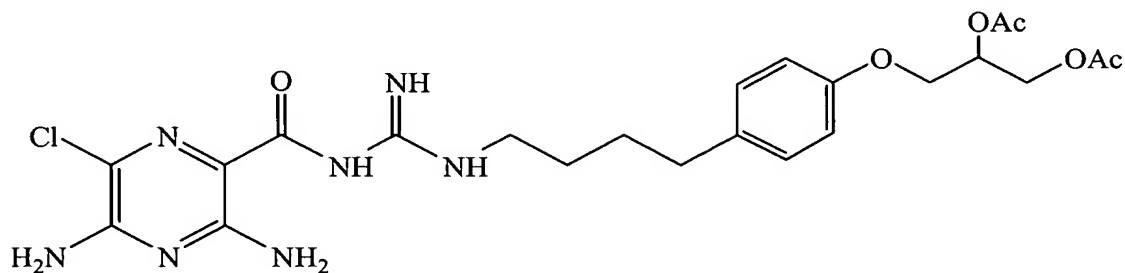179. (New) The method of Claim 177, wherein the compound is represented by the formula:

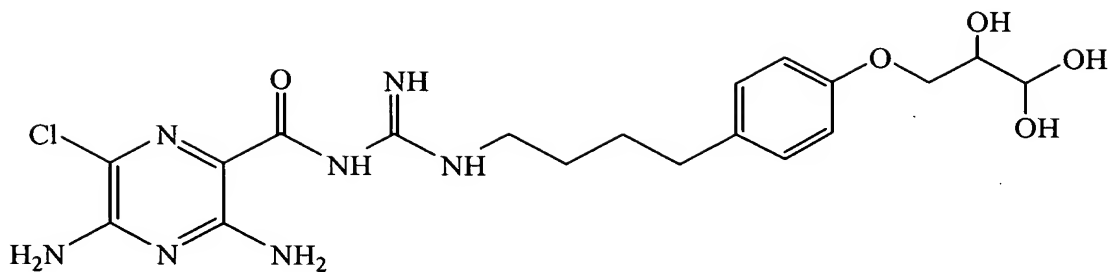180. (New) The method of Claim 177, wherein the compound is represented by the formula:

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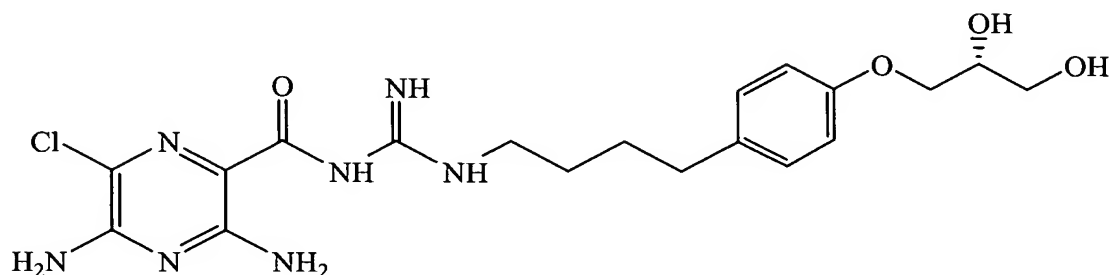181. (New) The method of Claim 177, wherein the compound is represented by the formula:

182. (New) The method of Claim 177, wherein the compound is represented by the formula:

183. (New) The method of Claim 161, wherein R^5 is $-(CH_2CH_2O)_m-R^8$.

184. (New) The method of Claim 161, wherein R^5 is $-O-(CH_2CH_2O)_m-R^8$.

185. (New) The method of Claim 184, wherein the compound is represented by the formula:

186. (New) The method of Claim 184, wherein the compound is represented by the formula:
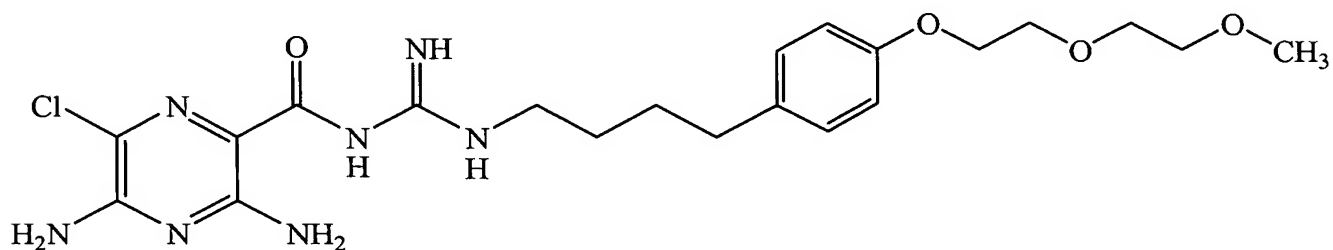
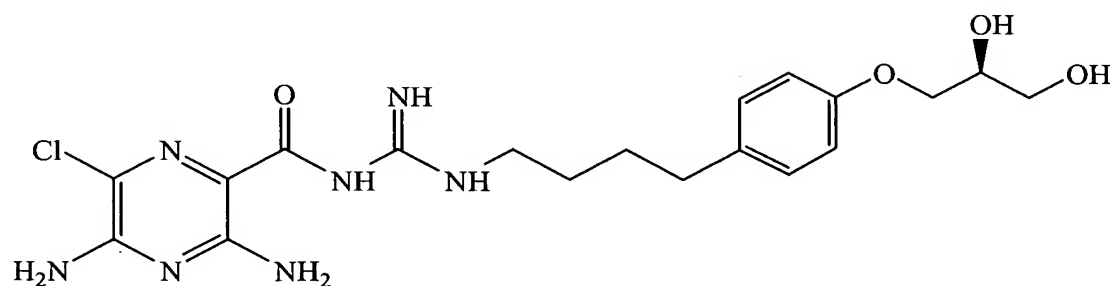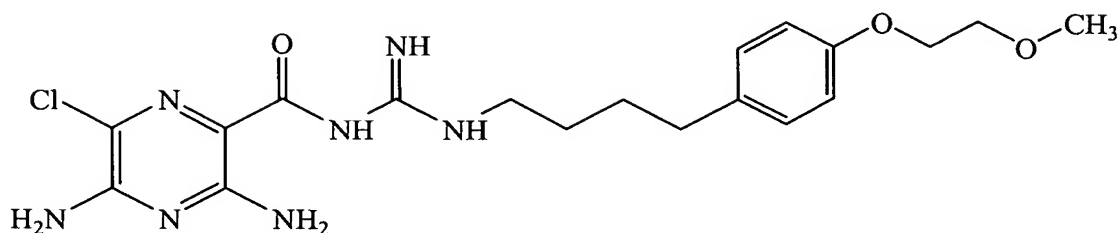187. (New) The method of Claim 184, wherein the compound is represented by the formula:
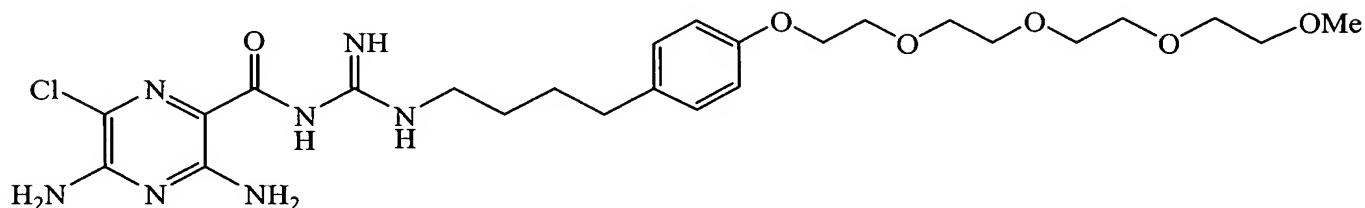
188. (New) The method of Claim 161, wherein R^5 is $-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$.

189. (New) The method of Claim 161, wherein R^5 is $-O-(CH_2CH_2O)_m-CH_2CH_2NR^7R^{10}$.

190. (New) The method of Claim 161, wherein R^5 is $-(CH_2)_n-C(=O)NR^7R^{10}$.

191. (New) The method of Claim 161, wherein R^5 is $-O-(CH_2)_m-C(=O)NR^7R^{10}$.

192. (New) The method of Claim 161, wherein R^5 is $-(CH_2)_n-(Z)_g-R^7$.

193. (New) The method of Claim 161, wherein R^5 is $-O-(CH_2)_m-(Z)_g-R^7$.

194. (New) The method of Claim 193, wherein the compound is represented by the formula:

195. (New) The method of Claim 193, wherein the compound is represented by the formula:
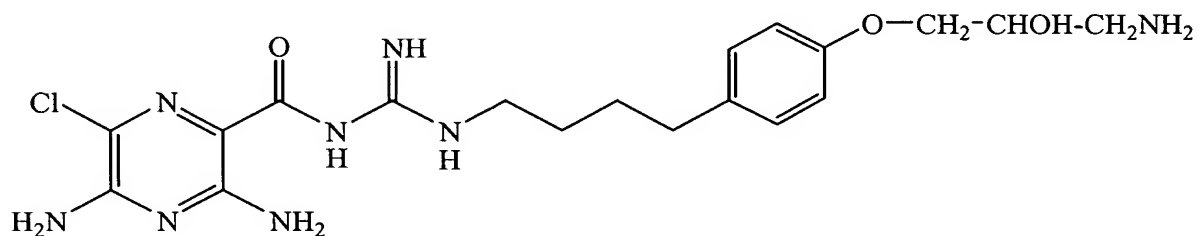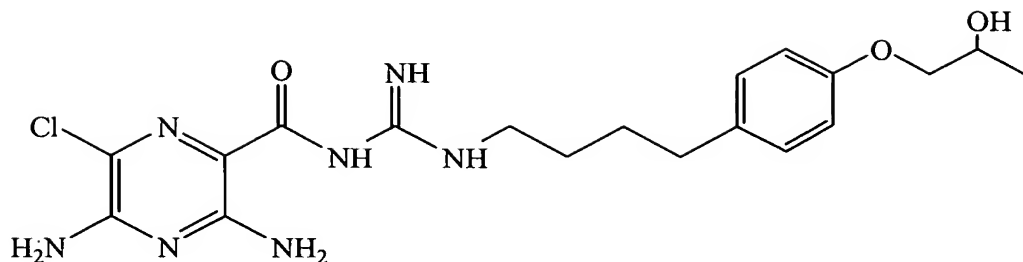
The chemical structure at the top shows a chloro-diamino-pyrazine carboxamide guanidine compound with a 4-substituted phenyl ether bearing a hydroxypropyl group.

196. (New) The method of Claim 161, wherein R^5 is-$(CH_2)_n$-NR^{10}-$CH_2(CHOR^8)(CHOR^8)_n$-CH_2OR^8.

197. (New) The method of Claim 161, wherein R^5 is -O-$(CH_2)_m$-NR^{10}-$CH_2(CHOR^8)(CHOR^8)_n$-CH_2OR^8.
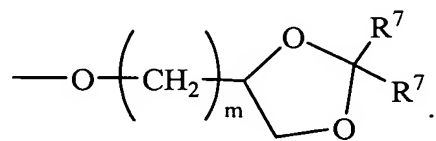
198. (New) The method of Claim 161, wherein R^5 is -O-$(CH_2)_m$-CO_2R^7.

199. (New) The method of Claim 161, wherein R^5 is -OSO_3H.

200. (New) The method of Claim 161, wherein R^5 is -O-glucuronide.

201. (New) The method of Claim 161, wherein R^5 is -O-glucose.

202. (New) The method of Claim 161, wherein R^5 is

203. (New) The method of Claim 202, wherein the compound is represented by the formula:
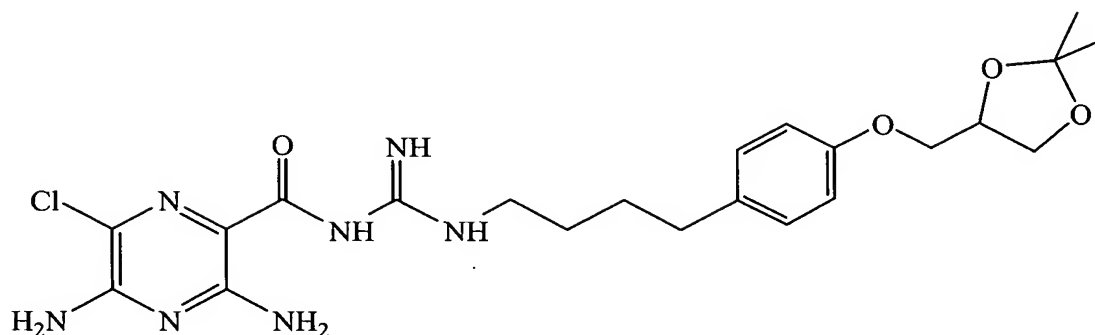
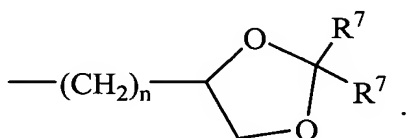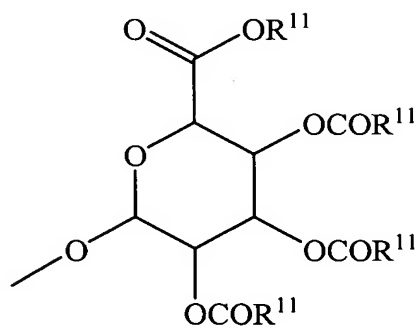204. (New) The method of Claim 161, wherein R^5 is

205. (New) The method of Claim 161, wherein R^5 is

206. (New) The method of Claim 205, wherein the compound is represented by the formula:
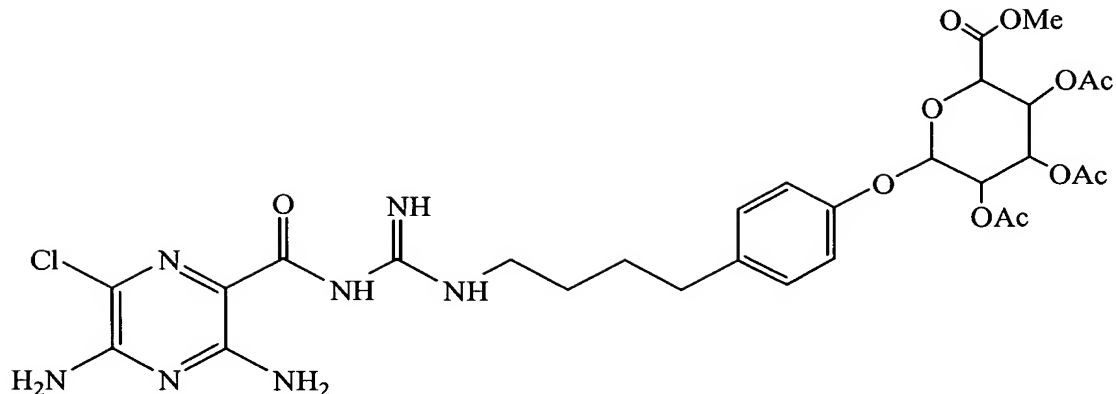
207. (New) The method of Claim 125, wherein

X is halogen;

Y is -N(R^7)$_2$;

R^1 is hydrogen or C$_1$-C$_3$ alkyl;

R^2 is -R^7, -(CH$_2$)$_m$-OR^8, or -(CH$_2$)$_n$-CO$_2$R^7;

R^3 is a group represented by formula (A); and

R^4 is hydrogen, a group represented by formula (A), or lower alkyl.

208. (New) The method of Claim 207, wherein

X is chloro or bromo;

Y is -N(R^7)$_2$;

R^2 is hydrogen or C$_1$-C$_3$ alkyl;

at most three R^6 are other than hydrogen as defined above;

at most three R^L are other than hydrogen as defined above; and

at most 2 Q in a ring are nitrogen atoms.

209. (New) The method of Claim 208, wherein Y is -NH$_2$.

210. (New) The method of Claim 209, wherein R^4 is hydrogen;

at most one R^L is other than hydrogen as defined above;

at most two R^6 are other than hydrogen as defined above; and

at most 1 Q in a ring is a nitrogen atom.

211. (New) The method of Claim 210, wherein no Q in a ring is a nitrogen atom.

212. (New) The method of Claim 125, wherein R^5 is $-(CH_2)_m-OR^8$.

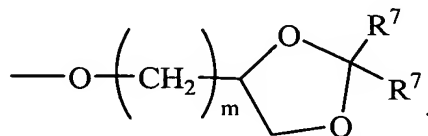213. (New) The method of Claim 125, wherein R^5 is $-O-(CH_2)_m-OR^8$.

214. (New) The method of Claim 125, wherein R^5 is $-(CH_2)_n-NR^7R^{10}$.

215. (New) The method of Claim 125, wherein R^5 is $-O-(CH_2)_m-NR^7R^{10}$.

216. (New) The method of Claim 125, wherein R^5 is
$-(CH_2)_n(CHOR^8)(CHOR^8)_n-CH_2OR^8$.

217. (New) The method of Claim 125, wherein R^5 is
$-O-(CH_2)_m(CHOR^8)(CHOR^8)_n-CH_2OR^8$.

218. (New) The method of Claim 125, wherein R^5 is $-(CH_2CH_2O)_m-R^8$.

219. (New) The method of Claim 125, wherein R^5 is $-O-(CH_2CH_2O)_m-R^8$.
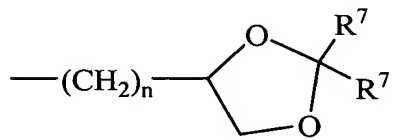
220. (New) The method of Claim 125, wherein R^5 is -$(CH_2CH_2O)_m$-$CH_2CH_2NR^7R^{10}$.

221. (New) The method of Claim 125, wherein R^5 is -O-$(CH_2CH_2O)_m$-$CH_2CH_2NR^7R^{10}$.

222. (New) The method of Claim 125, wherein R^5 is -$(CH_2)_n$-$C(=O)NR^7R^{10}$.

223. (New) The method of Claim 125, wherein R^5 is -O-$(CH_2)_m$-$C(=O)NR^7R^{10}$.

224. (New) The method of Claim 125, wherein R^5 is -$(CH_2)_n$-$(Z)_g$-R^7.

225. (New) The method of Claim 125, wherein R^5 is -O-$(CH_2)_m$-$(Z)_g$-R^7.

226. (New) The method of Claim 125, wherein R^5 is -$(CH_2)_n$-NR^{10}-$CH_2(CHOR^8)(CHOR^8)_n$-CH_2OR^8.

227. (New) The method of Claim 125, wherein R^5 is -O-$(CH_2)_m$-NR^{10}-$CH_2(CHOR^8)(CHOR^8)_n$-CH_2OR^8.

228. (New) The method of Claim 125, wherein R^5 is -O-$(CH_2)_m$-CO_2R^7.

229. (New) The method of Claim 125, wherein R^5 is -OSO_3H.

230. (New) The method of Claim 125, wherein R^5 is -O-glucuronide.

231. (New) The method of Claim 125, wherein R^5 is -O-glucose.

232. (New) The method of Claim 125, wherein R^5 is

$$-O-(CH_2)_m-\overset{O-}{\underset{O-}{\langle}}\overset{R^7}{\underset{R^7}{\rangle}}.$$

233. (New) The method of Claim 125, wherein R^5 is

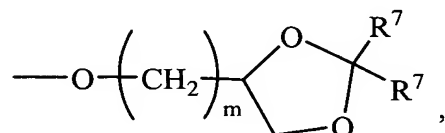$$-(CH_2)_n-\overset{O-}{\underset{O-}{\langle}}\overset{R^7}{\underset{R^7}{\rangle}}.$$

234. (New) The method of Claim 125, wherein R^5 is
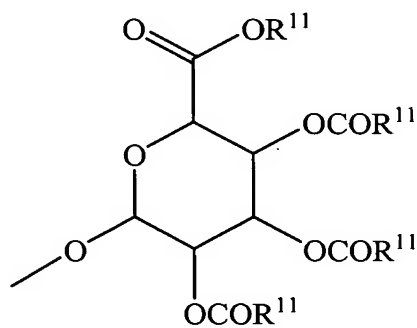
235. (New) The method of Claim 125, wherein R^5 is selected from the group consisting of

$-O-(CH_2)_3-OH$, $-NH_2$, $-O-CH_2-(CHOH)_2-CH_2OH$, $-O-CH_2-CHOH-CH_2OH$,

-O-CH₂CH₂-O-tetrahydropyran-2-yl, -O-CH₂CHOH-CH₂-O-glucuronide,

-O-CH₂CH₂OH, -O-(CH₂CH₂O)₄-CH₃, -O-CH₂CH₂OCH₃,

-O-CH₂-(CHOC(=O)CH₃)-CH₂-OC(=O)CH₃, -O-(CH₂CH₂O)₂-CH₃,

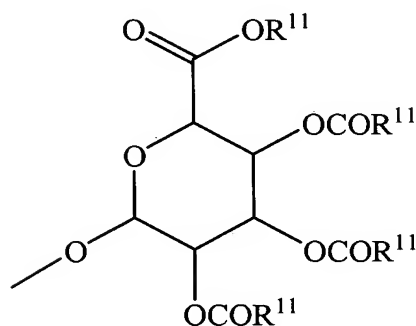-OCH₂-CHOH-CHOH-CH₂OH, -CH₂OH, -CO₂CH₃,

and

236. (New) The method of Claim 125, wherein R^5 is selected from the group

consisting of para -O-(CH₂)₃-OH, para -NH₂, para -O-CH₂-(CHOH)₂-CH₂OH, ortho -O-CH₂-

CHOH-CH₂OH, meta -O-CH₂-CHOH-CH₂OH, para -O-CH₂CH₂-O-tetrahydropyran-2-yl,

para -O-CH₂CHOH-CH₂-O-glucuronide, para -O-CH₂CH₂OH, para -O-(CH₂CH₂O)₄-CH₃,

para -O-CH₂CH₂OCH₃, para -O-CH₂-(CHOC(=O)CH₃)-CH₂-OC(=O)CH₃, para -O-

(CH₂CH₂O)₂-CH₃, -OCH₂-CHOH-CHOH-CH₂OH, para -CH₂OH, para -CO₂CH₃, para -

SO₃H, para -O-glucuronide, para

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$$-O-(CH_2)_m-\overset{\displaystyle O}{\underset{\displaystyle O}{\diagdown}}\overset{R^7}{\underset{R^7}{\diagup}}$$

and

para

$$\text{(structure with pyranose ring bearing } OR^{11}, OCOR^{11}, OCOR^{11}, OCOR^{11}\text{)}$$
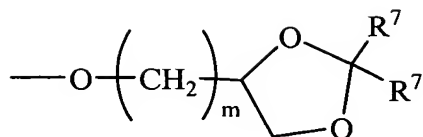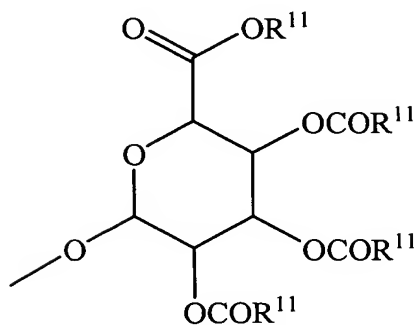
237. (New) The method of Claim 235, wherein

X is chloro or bromo;

Y is $-N(R^7)_2$;

R^1 is hydrogen or C_1-C_3 alkyl;

R^2 is hydrogen or C_1-C_3 alkyl;

R^3 is a group represented by formula (A); and

R^4 is hydrogen, a group represented by formula (A), or lower alkyl;

at most three R^6 are other than hydrogen as defined above; and

at most three R^L are other than hydrogen as defined above.

238. (New) The method of Claim 237, wherein

R^4 is hydrogen;

at most one R^L is other than hydrogen as defined above; and

at most two R^6 are other than hydrogen as defined above.

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239. (New) The method of Claim 236, wherein

X is chloro or bromo;

Y is $-N(R^7)_2$;

R^1 is hydrogen or C_1-C_3 alkyl;

R^2 is hydrogen or C_1-C_3 alkyl;

R^3 is a group represented by formula (A); and

R^4 is hydrogen, a group represented by formula (A), or lower alkyl;

at most three R^6 are other than hydrogen as defined above; and

at most three R^L are other than hydrogen as defined above.

240. (New) The method of Claim 239, wherein

R^4 is hydrogen;

at most one R^L is other than hydrogen as defined above; and

at most two R^6 are other than hydrogen as defined above.

241. (New) The method of Claim 125, wherein x is a single bond.

242. (New) The method of Claim 125, wherein the compound is in the form of a pharmaceutically acceptable salt.

243. (New) The method of Claim 125, wherein the compound is in the form of a hydrochloride salt.

244. (New) The method of Claim 125, wherein the compound is in the form of a mesylate salt.

245. (New) The method of Claim 125, wherein the compound is administered as a pharmaceutical composition which also comprises a acceptable carrier.

246. (New) The method of Claim 125, wherein the compound is administered as a pharmaceutical composition which also comprises a bronchodilator.

SUPPORT FOR THE AMENDMENTS

The Title of the application has been amended.

Continuing application data has been added to page 1.

The amendment at page 39 corrects an obvious error in chemical the structure of the compound over the first arrow. There should be an oxygen atom adjacent to the ClC(=O) group.

A substitute Abstract has been submitted.

Newly added Claims 125-246 are supported by the specification at pages 4-72 and by original Claims 1-124.

No new matter is believed to have been added to this application by the amendments submitted above.